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10/551,340	09/28/2005	Tadashi Yamazaki	081356-0249	4619

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FOLEY AND LARDNER LLP
SUITE 500
3000 K STREET NW
WASHINGTON, DC 20007

EXAMINER	
FOSTER, CHRISTINE E	

ART UNIT	PAPER NUMBER
1641	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/551,340	YAMAZAKI ET AL.	
	Examiner	Art Unit	
	Christine Foster	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 February 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *11-15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11-15* is/are rejected.

7)☒ Claim(s) *11* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *28 September 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Amendment Entry

1. Applicant's amendment, filed 2/18/2009, is acknowledged and has been entered. Claims 1-10 were canceled. New claims 11-15 have been added. Accordingly, claims 11-15 are currently pending and subject to examination below.

2. In the interest of expediting prosecution, Applicant's submission has been accepted. However, Applicant is reminded of the proper format for amendments to the specification. In the instant case, it is noted that the amendments to the specification on pages 7-8 are presented with markings suggesting that the words "glutamine" and "asparagine" are currently being removed. This is improper because these terms were previously removed by amendment on 4/23/2008. Amendments should be presented with markings to indicate the changes that have been made *relative to the immediate prior version*. See MPEP 714.

Priority

3. The present application was filed on 9/28/05 and is a National Stage (371) application of PCT/JP04/04606, filed 3/31/04. Acknowledgment is also made of applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d) to Japanese Application No. 2003-094059, filed on 3/31/03.

Objections/ Rejections Withdrawn

4. The objection to the specification as containing new matter is withdrawn in response to Applicant's persuasive arguments (Reply, pages 4-5).

5. The objection to the specification for informalities has been obviated by Applicant's amendments.

6. The objections to and rejections of claims 1-6 have been withdrawn in response to Applicant's cancellation of these claims.

Specification

7. The disclosure is objected to because of the following informalities:

8. On page 7, line 11, the specification discloses "0.16 **mg**" which appears to be an obvious error of "0.16 **mg/ml**".

Claim Objections

9. Claim 11 is objected to because of the following informalities:

10. Claim 11, lines 2-3 refer to "latex particles, which are coated anti-lipoprotein(a) antibody", which should apparently read --which are coated with anti-lipoprotein(a) antibody--.

11. The sentence structure of claim 11, part (i) may present confusion. In particular, it appears that Applicant intends that "and with a basic amino acid…" refers back to the step of effecting a mixture. In other words, a mixture is effected which is a mixture of sample, latex particles (which are coated with antibody), and a basic amino acids. However, because the phrase "and with a basic amino acid…" is placed following "which are coated [with] anti-lipoprotein(a) antibody", the claim could be misinterpreted as meaning that the particles are coated with antibody and with a basic amino acid. It is suggested that the claim be reworded for clarity.

Claim Rejections - 35 USC § 112

12. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

13. Claims 11-15 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. *This is a new matter rejection.*

14. New claim 11 recites that the amount of antibody present in the mixture is "**about** 0.15 mg/ml or greater". Dependent claim 12 recites the specific range of "**about** 0.15 mg/ml to about 0.23 mg/ml".

In addition, claim 11 also refers to the amount of basic amino acid that is present in the mixture as being "**about** 12% by weight or greater"; dependent claim 13 recites "**about** 12% to about 17% by weight".

Applicant states that support for the claims may be found at pages 2 and 7-9 as well as in the original claims (Reply, page 4).

In regards to the antibody concentration, the specification discloses the ranges of "greater than or equal to at least 0.15 mg/ml", "preferably greater than or equal to 0.16 mg[/ml]" (page 7, first full paragraph). The specification also states that an upper limit is not limited but that the

concentration is "preferably 1 mg/mL or less, more preferably 0.3 mg/mL or less, particularly preferably 0.23 mg/mL or less" (ibid).

However, it is noted that the disclosed ranges are not qualified by the term "about". Similarly, the claims as originally filed recited precise rather than approximate ranges. The insertion of the term "about" into the claimed ranges therefore broadens the scope of the original disclosure so as to encompass a genus of values. In the case of the upper limit of the claimed range (0.23 mg/ml), the disclosures of antibody concentrations of 0.3 mg/ml or less and of 0.1 mg/ml or less do reasonably provide a suggestion of values that may be higher than 0.23 mg/ml.

However, in the case of the lower end of the claimed ranges, it is noted that "about" 0.15 mg/ml would encompass values not only slightly higher but also slightly lower. There is no direction in the specification to employ values lower than 0.15 mg/ml, and there is also no suggestion that the disclosed lower limit of 0.15 mg/ml is intended to be approximate.

Furthermore, specification discloses that the final concentration of antibody added to a reaction system in typical prior art turbidimetric immunoassay methods is "0.05 to 0.1 mg/ml" (page 7, first full paragraph). In addition, arguments made in the instant Reply suggest that Applicant believes that the high concentrations of antibody and basic amino acid used in the claimed methods may have unexpected results (Reply, page 6, last paragraph). Such statements indicate that the present system may be characterized by unpredictability. Put another way, Applicant apparently believes that there is a substantive difference in results when using an antibody concentration of 0.1 mg/ml vs. 0.15 mg/ml. Although the specification contemplates antibody concentrations of 0.15 mg/ml or greater, the recited range of "about" 0.15 mg/ml encompasses a genus of values not only greater than but all less than this value. If changes in

antibody concentration of 0.05 mg/ml do indeed result in a substantive change in assay results, it is not apparent what values lower than 0.15 mg/ml could be successfully used while maintaining the desired results. Applicant has not disclosed a representative number of species (of values of "about" 0.15 mg/ml) to adequately represent or describe the claimed genus.

Similarly, with regard to the concentration of basic amino acid, it is acknowledged that the specification discloses the ranges of "greater than or equal to 12%, preferably greater than or equal to 15%", "on the order of 40%", "preferably 25% or less, more preferably 20% or less, particularly preferably 17% or less" (see the paragraph bridging pages 7-8). Specific concentrations of 15%, 16.7%, and 17% are exemplified (Examples 1-2).

As above, however, the specification does not qualify these ranges using the term "about" as now claimed. Values somewhat higher than 17% can be reasonably envisaged from the disclosure of concentrations that may be "preferably 25% or less, more preferably 20% or less". However, the insertion of the term "about" in the context of the lower end of the range ("about 12% by weight") broadens the scope of the original disclosure so as to now encompass values not only slightly higher but also slightly lower than 12%.

The specification does not direct the skilled artisan to employ values lower than 12% or indicate that this value is intended to be approximate. In fact, when the basic amino acid arginine was employed in Example 2, it appears that differing results were obtained when a concentration of 10% was used as compared to concentrations of 15% or 17%. In addition, arguments made in Applicant's reply suggest that Applicant believes that the high concentrations of antibody and basic amino acid used in the claimed methods may have unexpected results (Reply, page 6, last paragraph). Such statements indicate that the present system may be characterized by

unpredictability. As above, if employing a concentration of 12% does indeed result in a substantive difference in results as compared to a concentration of 10%, it is not apparent what other values falling within the genus of "about" 12% would also result in the desired results. As such, the genus now claimed has not been adequately described in the specification.

For all of these reasons, the insertions of the term "about" into the claimed ranges represent broadening amendments unsupported by the specification as originally filed.

Claim Rejections - 35 USC § 103

15. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

16. Claims 11-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Borque et al. ("Automated turbidimetry of serum lipoprotein(a)" Eur J Clin Chem Clin Biochem. 1993 Dec;31(12):869-74) in view of de Steenwinkel et al. (US 4,362,531), Metzner et al. (US 6,447,774), and Schmitdberger et al. (US 5,180,679).

Borque et al. teaches a turbidimetric immunoassay for quantifying lipoprotein(a) using latex particle agglutination (abstract and especially at page 869, "Summary"). The immunoassay employs rabbit polyclonal IgG antiserum against human lipoprotein(a), which is added to the assay system as part of a latex reagent in which the antibody is coated onto latex particles (pages 869-870, "Antibody", "Latex reagent", "Assay Procedure" and "Latex nephelometric assay"). The amount of lipoprotein(a) is then determined by observing the mixture for turbidity due to

latex particle agglutination using an automatic analyzer (see page 870, "Assay procedure"; page 871, "Correlation"; and page 872, right column).

The teachings of Borque et al. differ from the claimed invention in that (1) the reference fails to specifically teach adding a basic amino acid to the assay system and (2) the reference fails to specify the particular concentrations of the antibodies that were used in the assay.

With respect to (1), de Steenwinkel et al. also relates to particle agglutination immunoassays and teaches that undesired interference effects in such assays due to non-specific protein-protein interactions can be reduced or overcome by including in the assay mixture a chaotropic or chaotropic-like agent (the abstract; column 1, lines 18-41; column 2, line 42 to column 4, line 50). However, de Steenwinkel et al. do not specifically exemplify chaotropic agents that are basic amino acids.

Metzner et al. teaches that known chaotropic agents include arginine (column 1, lines 55-56; column 2, lines 12-13).

Therefore, it would have been obvious to one of ordinary skill in the art to add a chaotropic agent to the agglutination immunoassay of Borque et al. because de Steenwinkel et al. taught that such agents reduce or overcome interferences in particle agglutination immunoassays. It would have been further obvious to employ the basic amino acid arginine as the chaotropic agent in the method of Borque et al. and de Steenwinkel et al. because Metzner et al. taught that arginine is known to be a chaotropic agent. The selection of a known material for its known purpose would have been obvious.

Furthermore, de Steenwinkel et al. teach that the amount of chaotropic agent to be added to agglutination immunoassays should be checked for individual cases, since the optimum

amount may vary (column 3, lines 29-38). Such teachings indicate that the amount of a chaotropic substance was recognized to be a result-effective variable. Consequently, and absent evidence of criticality for the currently claimed amounts, it would have been obvious to one of ordinary skill in the art to arrive at the claimed amounts (i.e., about 12% by weight or greater) out of the course of routine optimization.

With respect to (2), Borque et al. indicate that the amount of antibody added was adjusted by providing antibody in a protein/ latex ratio of 1/10; 30 ml of a 0.5% particle solution was then added to the assay (page 870, "Latex Reagent" and "Assay procedure"). However, Borque et al. does not explicitly state what the final concentration of the antibody in the assay mixture was.

Schmidtberger et al. also relates to particle agglutination immunoassays and teaches that different amounts of antibody can be bound to the particles in order to influence the time at which agglutination occurs (column 2, lines 13-62).

Therefore, given that the amount of antibody used in a particle agglutination immunoassay was recognized in the art to be a result-effective variable (as taught by Schmidtberger et al.), it would have been further obvious to one of ordinary skill in the art to employ polyclonal IgG antiserum against human lipoprotein(a) at the claimed concentrations (i.e., about 0.15 mg/ml or greater) out of the course of routine optimization.

One would have had a reasonable expectation of success because de Steenwinkel et al. is directed to the effects of chaotropic substances on agglutination assays for analytes in general (column 4, lines 44-50).

With respect to claim 15, Borque et al. teaches a polyclonal antibody (see page 869, "Antibody").

Response to Arguments

17. With respect to the rejections under § 103, it is noted that Applicant's arguments are technically moot as they pertain to the rejections of claims 1-6, which are now canceled. However, certain of Applicant's arguments have been addressed below as they pertain to the new grounds of rejection set forth above.

18. *Applicant argues that the claimed invention involves an antibody concentration of at least 0.15 mg/ml, while conventional antibody concentrations typically range from 0.05 to 0.1 mg/ml* (Reply, page 6, third paragraph).

This is not found persuasive because initially, the Examiner notes that the specification does not provide a specific or limiting definition for the term "about" in the context of antibody concentration. Consequently, "about 0.15 mg/ml" is not seen to clearly rule out 0.1 mg/ml, for example.

In addition, while the evidence of the specification has been considered, it is not seen as sufficient to establish that the claimed antibody concentrations would be thought of as atypically large or unusual by a person of ordinary skill in the art. To the contrary, Schmitdberger et al. teach antibody concentrations of 2.2-3.3 mg/ml in latex agglutination assays (see in particular claim 4). More generally, antibody concentration was well recognized in the art at the time of the invention to be a result-effective variable, one which was frequently optimized when conducting immunoassays (as taught for example by Schmidtberger et al.). Applicant has not provided any comparative data to establish criticality for the currently claimed amounts of "about 0.15 mg/ml

or greater". Absent such evidence, it is maintained for reasons of record that it would have been obvious to arrive at the claimed amounts out of the course of routine optimization.

19. *Applicant argues that the present claims require a basic amino acid concentration that is about 12% or greater, whereas the prior art illustrated by Metzner discloses addition of arginine at the much lower concentrations of 2% and 5%* (Reply, page 6, third paragraph). *Applicant argues that de Steenwinkel cautions that high concentrations of chaotropic agents, such as the basic amino acid arginine, is deleterious to immunoassays* (Reply, page 6, last paragraph).

This is not found persuasive because as above, Applicant has not advanced evidence of criticality for the currently claimed amounts of basic amino acid. Applicant argues for a "surprising result of detecting a broader range of lipoprotein(a) phenotypes" (Reply, page 6, last paragraph) but has not adequately documented the existence of unexpected results. The arguments of counsel cannot take the place of factually supported objective evidence.

Moreover, the teachings of Metzner et al. and de Steenwinkel to which Applicant points do not rise to the level of a teaching away. Metzner et al. exemplifies specific amounts of arginine to be used in tissue preparations; one of ordinary skill in the art would not understand such amounts to be universally applicable to any type of method employing arginine, such as an immunoassay. Therefore, this is seen as at best a teaching away from using other amounts of arginine when preparing tissue preparations.

In regards to de Steenwinkel et al., the reference does not disparage or otherwise discourage the use of the claimed amounts, but merely suggests that for any particular immunoassay mixture there will be an optimal amount which must be determined in each case by trial and experiment (de Steenwinkel, column 3, lines 23-37). Nowhere does de Steenwinkel

et al. caution against using amounts such as those claimed. Nonetheless, the reference clearly indicates that the amount of chaotropic agent was recognized in the art to be a result-effective variable.

Therefore, Applicant's arguments that the prior art teaches away from the claimed amounts of basic amino acid are not persuasive. In fact, it is noted that de Steenwinkel et al. teach that in most cases, amounts of chaotropic agent from about **0.5 up to about 2M** are satisfactory (column 3, lines 34-36). In the case of the chaotropic agent arginine, a 12% weight corresponds to approximately 0.8M[1], which falls squarely within the claimed range suggested by de Steenwinkel et al.

Absent evidence of criticality for the currently claimed amounts, therefore, it is maintained for reasons of record that it would have been obvious to arrive at the claimed amounts out of the course of routine optimization as specifically suggested by de Steenwinkel.

20. *Applicant further argues that Schmidtberger does not contemplate adjusting antibody concentration to alter antigen detection or to allow for measuring a plurality of lipoprotein(a) phenotypes* (Reply, page 7, second paragraph).

This is not found persuasive because the fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985). In the instant case, although

[1] To convert weight % to molarity, assume 100 g of solution, a solution density of 1.19 g/mL for water, and a formula weight of 172. g/mol for arginine (Arg):
12%weight solution = 12g Arg + 88 g H_2O
L solution = 100 g solution x (1 ml/1.19 g) x (1L/1000ml) = 0.084 L solution
Moles Arg = 12 g Arg x (1 mol Arg/172.2 g/mol Arg) = 0.069 moles
Molarity of a 12% weight solution of Arg = (0.069 moles/ 0.0840 L solution) = 0.82 M

Schmidtberger does not specifically teach adjusting the antibody concentration for the particular purpose mentioned, the reference clearly establishes antibody concentration to be a result-effective variable. It is therefore maintained for reasons of record that it would have been obvious to arrive at the claimed amounts out of the course of routine optimization.

Conclusion

21. Claims 11-15 are rejected.

22. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christine Foster whose telephone number is (571) 272-8786. The examiner can normally be reached on M-F 6:30-3:00. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mark Shibuya, can be reached at (571) 272-0806. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Christine Foster/
Examiner, Art Unit 1641

/Christopher L. Chin/
Primary Examiner, Art Unit 1641